Claim 1 is rejected because it is alleged that the claim, drawn to a method of analyzing a sample, provides two polypeptides but does not provide a sample. Further, the Examiner indicates that the numbering of the subsections of the claim is confusing. Applicants have amended the claim to include letter designations (a) – (e) on the individual steps of the claim. Further, the claim has been amended to recite step (d), "contacting said immobilized polypeptide or said binding partner polypeptide with said sample." Applicants submit that the amended claim provides a sample and clearly states the individual steps of the claimed method. Applicants respectfully request the withdrawal of the §112, second paragraph rejection of claim 1 as amended.

Dependent claims 2-4 are rejected because the phrase "the binding partner" allegedly lacks proper antecedent basis in claim 1. The amendment of claim 1 which replaces the term "second polypeptide" with the term "binding partner" in steps (a), (c), and (e) is sufficient to overcome this rejection. Support for the amended language is found at page 4, lines 15-18, which define "binding partner" polypeptides as polypeptides that bind to an immobilized polypeptide. Applicants respectfully request the withdrawal of this §112, second paragraph rejection of claims 2-4 as amended.

Dependent claim 4 is rejected because the phrase "said labels" allegedly lacks proper antecedent basis in claim 3, from which it depends. The claim has been amended to recite "wherein said label on said immobilized polypeptide is different from said label on said binding partner polypeptide." Applicants submit that all terms of claim 4 as amended have proper antecedent basis. Applicants respectfully request the withdrawal of this §112, second paragraph rejection of claim 4 as amended.

Dependent claim 6 is rejected because the phrase "said detectable signal" allegedly lacks antecedent basis in claims 3 and 4, from which it depends. Applicants submit that the amendment of "said detectable signal" to "a detectable signal" in claim 6 is sufficient to overcome the alleged lack of antecedent basis for the term. Claim 6 is also rejected because the phrase "between the labels" allegedly lacks antecedent basis in claim 3. Applicants submit that the amendment of claim 6 to recite "between the label on said immobilized polypeptide and the label on said second polypeptide" provides proper antecedent basis to all terms in claim 6 with respect to both amended claims 3 and 4, from which it depends. Applicants respectfully request the withdrawal of the §112, second paragraph rejections of claim 6 as amended.

Dependent claim 8 is rejected because the phrase "the hybrid species" allegedly lacks proper antecedent basis in claim 1. Applicants submit that the deletion of the term "hybrid" in amended claim 8 is sufficient to overcome this rejection. Claim 8 has also been amended to replace the term "second polypeptide" with "binding partner polypeptide" in order to agree with the amended antecedent term in claim 1. Applicants respectfully request the withdrawal of the §112, second paragraph rejection of claim 8 as amended.

Dependent claim 12 is rejected because the "wherein" clause allegedly does not recite an active methods step. The Office Action states that the nature and type of the antibody used in the assay is not defined, and which of the polypeptides or the product of the polypeptides the antibodies bind is not distinctly claimed. Further, the Office Action states that it is not clear how the antibody that need not be specific to any of the components interacts with the polypeptides to produce a measurement. Applicants submit that claim 12 as amended recites an active methods step comprising "measuring association using an antibody." Further, claim 12 as amended recites an antibody "that binds to said first or said binding partner polypeptide." As amended, therefore, the recited antibody is of a type that binds a specific component of the assay, namely the first polypeptide or its binding partner. Support for the language of this amendment is found at page 22, line 29 to page 23, line 3. Applicants respectfully request the withdrawal of the §112, second paragraph rejection of claim 12 as amended.

Dependent claim 13 is rejected for lack of proper antecedent basis in reference to "step (d)" in claim 1, because claim 1 does not contain a step (d). Claim 1 is amended herein above to recite steps (a) – (e). Claim 13 as amended herein refers to step (e) of claim 1, which recites "contacting said immobilized polypeptide or said binding partner polypeptide with said sample."

The Office Action also states that the agent used to modify one or both of the polypeptides in claim 13 is not defined, and the functional characteristics or types of modifications by the agent are not distinctly claimed. Applicants submit that claim 13 as amended recites an agent capable of "*covalently*" modifying one or both of the polypeptides. As amended, the modifying agent recites distinct functional characteristics and type of modification. Applicants therefore respectfully request the withdrawal of the §112, second paragraph rejection of claim 13 as amended.

Dependent claim 14 is rejected for allegedly not distinctly claiming the type of modification of the first polypeptide. Applicants submit that the amendment of claim 14 to recite

that the immobilized polypeptide is susceptible to enzymatic modification is sufficient to overcome this rejection. Applicants respectfully request the withdrawal of the §112, second paragraph rejection of claim 14 as amended.

Dependent claim 16 is rejected for referring to the "modification of step (d)" in claim 1 for lack of proper antecedent basis because claim 1 does not contain a step (d). As noted above, claim 1 now recites steps (a) – (e). This amendment of claim 1 and the amendment of claim 16 to refer to step (e) is sufficient to overcome this ground of rejection.

Claim 16 is also rejected for allegedly having an improper Markush group, and because "how assaying is measured is not distinctly claimed." The amendment of claim 16 to recite "assaying a modification selected from the group consisting of" and to recite "sentrinization, ADP-riobosylation, *and* the reversal of any of these modifications" places the alternative modifications in proper Markush group format. Applicants submit that assays for the modifications recited are known in the art or are found in the specification at: page 4, lines 6-13; page 47, line 5 to page 51, line 4; page 9, lines 6-11; page 69, line 1 to page 73, line 8; page 89, line 20 to page 97, line 14; page 52, lines 1-27; page 74, line 25 to page 88, line 7; page 88, line 13 to page 89, line 16; and page 97, line 17 to page 99, line 28. Applicants respectfully request the withdrawal of the §112, second paragraph rejection of claim 16 as amended.

Claim 18 is rejected because it is allegedly unclear whether the two detecting steps for modulation of binding of the polypeptides are one in the same. Applicants submit that the amendment of claim 18 to distinguish "detecting modulation of binding of the polypeptides *in the presence of the candidate modulator"* from detecting the reference signal modulation, is sufficient to overcome this rejection. Applicants respectfully request the withdrawal of the §112, second paragraph rejection of claim 14 as amended.

Rejections under 35 U.S.C. §102

Claims 1-8, 12-14, 16 and 18 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Bronstein et al., U.S. Patent No. 5,849,495. The Office Action states that Bronstein et al. disclose a method of analyzing a sample for the presence of a biopolymer in the sample, wherein the method comprises providing a polypeptide pair, specifically streptavidin and biotin. Applicants respectfully disagree.

First, biotin is not a polypeptide, which means that biotin and streptavidin are not a "polypeptide pair," as required by the instant claims. Therefore, step (a) of amended claim 1 is not satisfied by the cited portion of this reference.

Second, the biotinylated species is not a "polypeptide," but rather, a nucleic acid, DNA, as acknowledged in the Office Action in reference to particular embodiments. Therefore, the contacting of the immobilized, biotinylated DNA with a streptavidin-alkaline phosphatase conjugate is not contacting the "immobilized polypeptide" with the "second polypeptide" as recited in step (c) of claim 1 as amended.

Third, the Office Action equates energy transfer between CSPD and AttoPhos™ with the "interaction between" labels and "energy transfer" between labels recited in claims 6 and 7, respectively. However, the substrates CSPD and AttoPhos™ are not associated with a polypeptide as required by claims 2 or 3, from which claims 6 and 7 depend. There is energy transfer between the substrates, but because they are not labels associated with a polypeptide as required by claim 2 or 3, they do not "assay the modification of at least one of the polypeptides by measuring the association of the second polypeptide to the first polypeptide" as required by claim 1, from which claims 2, 3, 6 and 7 ultimately depend.

In view of the above, this embodiment in the Bronstein disclosure does not anticipate the invention of amended claim 1 or claims 2-8, 12-14 or 16 that depend from it.

The Office Action cites a second embodiment of the Bronstein disclosure cited as anticipating claims 1-7, 12-14, 16 and 18. In that embodiment, the Office Action states that the Hybritech Prostate Specific Antigen (PSA) kit, containing three different polypeptides, is used to determine the presence and amount of PSA in a sample. The three polypeptides are a PSA standard, an alkaline phosphatase-labeled mouse anti-PSA antibody and an anti-PSA capture antibody immobilized on a bead.

The Office Action states that the association of the alkaline phosphatase-labeled antibody with two different substrates resulted in the production of fluorescence and energy transfer from one modified component to another. Applicants traverse this rejection, as this embodiment of Bronstein et al. does not describe the invention as claimed. The fluorescence in this embodiment of the Bronstein disclosure results from the dephosphorylation of a 1,2-dioxetane (e.g., CSPD, BDMQ; see Examples 2 and 3, columns 15 and 16) and AttoPhos™ by the alkaline phosphatase. Each of these non-polypeptide species emits fluorescence upon dephosphorylation, and energy

transfer can occur from the 1,2-dioxetane to the AttoPhos™. The Office Action states that one of the antibodies was modified with alkaline phosphatase. However, the "modified components" cited in the Office Action are dephosphorylated 1,2-dioxetane and AttoPhos™ species, and thus are not modified polypeptides referred to in the claims and as they are defined in the present specification. The Examiner's use of the term "modified" is not consistent with the term as defined in the specification on page:

> Modification of a polypeptide may include proteolysis (proteolytic cleavage), phosphorylation, dephosphorylation (phosphatase), acylation (for example fatty acylation such as farnesylation, geranylgeranylation, myristoylation, palmitoylation), glycosylation, ubiquitination, prenylation, sentrinisation, ADP-ribosylation, or the reversal of these processes where these are possible. Preferably, the immobilised polypeptide may be a substrate for one or more of these enzymatic activities. The term 'modification' as used herein may also include the binding of one or more molecules of the test sample to a polypeptide. (page 4, lines 6-13)

The addition of alkaline phosphatase in the Bronstein reference is not encompassed by the term "modified" polypeptide in the instant claims as it is defined in the above-referenced passage. Furthermore, even if one assumes that the binding of, for example, PSA to anti-PSA antibody is a "modification" of the antibody according to the last sentence of the definition, the "modification" does not result in modulation of the association of the antibody and PSA as recited by the claim. Rather, the binding *is* the association. Therefore, Bronstein et al. does not meet the limitations of amended claim 1.

Independent claim 18 is also rejected under the "second" Bronstein embodiment, However, claim 18, drawn to a method for detecting or monitoring the activity of a modulator of a polypeptide modifying agent, also requires that the "modification of one or both of the polypeptides by the modifying agent results in modulation of the binding of the polypeptides to each other." Applicants submit that Bronstein et al. does not teach such modulation by "modification" of a polypeptide as the term "modified" is described in the above-referenced passage. If "modified," as it is described and defined in Applicant's specification and as required by the instant claims, was used in the Bronstein assay as it must be used in the instant claims, that is, if the binding of the anti-PSA antibody to the PSA modulated the binding of the immobilized capture antibody to PSA, the sandwich assay taught by Bronstein et al. would not

faithfully report the amount of PSA present, and the assay would be useless. Bronstein et al. therefore does not teach modification of one or both of the polypeptides by a modifying agent as recited in amended claim 18.

Claims 1-7, 14-16 and 18 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Tsien et al., U.S. Patent No. 5,439,797 (the '797 patent).

The Office Action states that the '797 patent discloses and claims a method of determining the concentration of an analyte in a sample, the method "carried out by utilizing first and second polypeptides that will associate with each other depending upon the presence, absence or amount of analyte present in the sample." The Office Action states further that both the first and the second polypeptides are fluorescently labeled in the '797 disclosure, that "the modification of the association of the first and second polypeptides is accomplished through fluorescence resonance energy transfer," and that the '797 disclosure teaches one of the polypeptides immobilized on a bead, concluding that the reference anticipates the presently claimed invention. Applicants respectfully disagree.

Applicants submit that the '797 patent does not teach a method of analyzing a sample comprising the step of "providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association," as required by claim 1 as amended. Specifically, neither of the polypeptides of the '797 disclosure is covalently (i.e., enzymatically) "modified," but rather the polypeptides bind to each other *only in the presence of cAMP*. Support for the "covalent" modification language of amended claim 1 is found on page 97, line 21 to page 98, line 8. Further, it is known in the art that all enzymatic reactions are covalent, based upon the definition of an enzyme:

> "A protein produced in a cell and capable of greatly accelerating by its catalytic action *the chemical reaction* of a substance (the substrate) for which it is often specific." (page 448, Dorland's Illustrated Medical Dictionary, 26th Ed., 1985, W.B. Saunders Co., Philadelphia; emphasis added; see Exhibit A)

Because the '797 patent does not disclose a method comprising the step of "providing a polypeptide pair comprising a first polypeptide and a binding partner polypeptide capable of associating, wherein the association of the polypeptides is detectable, and *covalent* modification of at least one of the polypeptides results in modulation of the association," it does not anticipate claim 1 as amended or any of claims 2-7 or 14-16 that depend from it. For the same reason,

amended claim 18, which also requires "first and second polypeptides capable of binding to each other wherein the covalent modification of one or both of the polypeptides by a modifying agent results in modulation of the binding of the polypeptides to each other," is not anticipated by the '797 patent disclosure. Applicants therefore respectfully request that the 35 U.S.C. §102(b) rejection of amended claim 1, claims 2-7 and 14-16 that depend from it ,and amended claim 18 over the '797 disclosure be withdrawn.

Claims 1-7 and 13-16 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Tsien et al., U.S. Patent No. 5,981,200 (the '200 patent). The Office Action states that the '200 patent discloses tandem fluorescent protein constructs for use in enzymatic assays conducted in 96 well microtiter plates, and that the reagents would associate with the surfaces of the 96 well plate "and therefore would be immobilized on the solid phase." The Office Action concludes that the '200 patent inherently teaches the use of a physical support on which the assay reagents can be immobilized. Further, the Office Action states that two different fluorescent labels are used in the assay method and are used in evaluating protease activity present in a sample. On this basis, the Office Action concludes that the '200 patent anticipates the presently claimed invention. Applicants respectfully disagree.

Applicants submit that the '200 patent does not expressly teach the immobilization of one of the polypeptides. The '200 patent merely mentions that assays may be performed in a microtiter plate format. The Office Action states:

> The reagents would associate with the surfaces of the 96 well plate and therefore would be immobilized on the solid phase (col 20, lines 47-54). As no specific type of immobilization of the first polypeptide is claimed, the disclosure of Tsien et al. inherently teaches the use of a physical support on which the assay reagents ***can be*** immobilized. (Emphasis added)

There are at least two reasons that this is incorrect. First, the cited passage merely makes reference to the possibility of performing the assay in a microtiter plate:

> According to one embodiment, a multi-axis translation stage moves a microtiter plate holding a plurality of samples in order to position different wells to be exposed. The multi-axis translation stage, temperature controller, auto-focusing feature, and electronics associated with imaging and data collection can be managed by an appropriately programmed digital computer. The computer also can transform the data collected during the assay into another format for presentation. ('200 patent, column 20, lines 47-54)

The reference does not teach <u>any</u> <u>reagent</u> immobilized on the plate.

Second, the Examiner states that the '200 patent inherently teaches the use of a physical support for reagent immobilization. Applicants submit that inherency is not applicable in the present rejection. The principle of inherency in anticipation was explained by the Federal Circuit Court in *Finnigan Corporation v. International Trade Commission,* 180 F.3d 1354,1365 (Fed. Cir. 1999) as follows:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co., U.S.A. v. Monsanto Co.*, 948 F.2d 1264 (Fed. Cir. 1991).
>
> *In re Oelrich* [citation omitted] states: Inherency, however, *may not be established by probabilities or possibilities*. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. (Emphasis added.)

That is, the mere possibility that reagents *can be* immobilized on a microtiter plate does not make immobilization inherent. This is the situation in which "a certain thing may result from a given set of circumstances." The Office Action provides no evidence making clear that the immobilization on the microtiter plate is necessarily present in the assay format described in the reference or that it would be so recognized by persons of ordinary skill. Applicants submit that one of ordinary skill in the art would not understand that placement of a solution containing a polypeptide into a well of a microtiter plate would necessarily result in association of such polypeptide with the surfaces of the plate resulting in immobilization of the polypeptide. The mere possibility of association with the surface of the wells is not sufficient to establish the inherency of polypeptide immobilization, therefore, Applicants submit that the '200 patent reference does not inherently teach the immobilization of the polypeptide. The '200 patent does not teach immobilizing the first polypeptide to a physical support, and such immobilization may not properly be said to be inherent in the format described by Tsien et al. Therefore, the reference does not teach every element of claim 1, and does not anticipate claim 1, as amended, or claims 2-7 and 13-16 that depend from it. Applicants therefore respectfully request that the §102(e) rejection of claims 2-7 and 13-16 over the '200 patent be withdrawn.

Claims 1-7 and 14 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Lakowicz et al. (U.S. Patent No. 5,631,169). The Office Action states that Lakowicz et al. discloses the use of polymeric supports for one reactant bound thereto and a second reactant

supplied in solution or suspension. Further, the Office Action states that samples are analyzed using first and second polypeptides, specifically antibodies, one of which is immobilized in the solid phase, and that each of the polypeptides is "labeled with different fluorescent labels that provide for assaying the modification of the polypeptides through the determination of the presence of absence of an antigen in the sample." Because energy transfer is used to monitor the interaction of antibody with antigen (the other antibody), the Office Action concludes that the reference anticipates the presently claimed invention. Applicants respectfully disagree.

The Lakowicz et al. reference does not teach "a polypeptide pair comprising a first polypeptide and a second polypeptide capable of associating, wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association," as required by claim 1 as amended. The Lakowicz reference teaches the interaction of two fluorescently labeled antibodies, one of which competes with an analyte for binding to the second antibody. There is no teaching of covalent modification of either antibody that modulates the interaction between the two antibodies. Therefore, Lakowicz et al. does not anticipate amended claim 1 or any of claims 2-7 and 14 that depend from it. Applicants therefore respectfully request that the §102(b) rejection over the Lakowicz et al. reference be withdrawn.

Claims 1-6, 10-14 and 18 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Gallatin et al., U.S. Patent No. 5,989,843 or 5,837,822. The Office Action states that Gallatin et al. discloses methods of analyzing samples utilizing a first polypeptide immobilized on a solid phase that interacts with a detectably labeled nonimmobilized binding partner, and that the presence or absence of bound label is correlated with the ability of a test agent to inhibit ICAM-R binding. Further, the Office Action states that fluorescent polystyrene beads are disclosed for the immobilization of a first polypeptide, the second polypeptide is labeled with a radioactive label, and a scintillation proximity assay is used to identify modulators of the first polypeptide's association with the second polypeptide. The method is said to be useful for identifying modulators of ICAM-R binding, and it is concluded that the reference anticipates the presently claimed invention. Applicants respectfully disagree.

Applicants submit that Gallatin et al. does not teach "a polypeptide pair comprising a first polypeptide and a second polypeptide capable of associating, wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in

modulation of the association," as required by amended claim 1 and claims dependent from it. Specifically, Gallatin et al. does not teach the covalent modification of either of the polypeptides that associate. As such, the reference does not teach the enzymatic modification of at least one of the polypeptides, as recited in claims 1 and 18 as amended. Therefore, the reference does not anticipate claim 1 as amended or claims 2-6 and 10-14 that depend from it, or claim 18 as amended. Applicants respectfully request that the §102(e) rejection over Gallatin et al. be withdrawn.

Claims 1 and 9 are rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Sehr, U.S. Patent No. 5,341,215. The Office Action states that the reference discloses a method for analyzing a sample for the presence of biomolecules, the method comprising the use of a solid phase coated with capture molecules complementary to the biomolecules. The Office Action further states that the biomolecules are antibody and antigen and are detected using surface plasmon resonance, concluding that the disclosure anticipates the presently claimed invention. Applicants respectfully disagree.

Applicants submit that Sehr et al. does not teach "a polypeptide pair comprising a first polypeptide and a second polypeptide capable of associating, wherein the association of the polypeptides is detectable, and covalent modification of at least one of the polypeptides results in modulation of the association," as required by claim 1 as amended. Specifically, similar to the previous references cited in the Office Action, the Sehr et al. reference does not teach covalent modification of at least one of the polypeptides, nor does it teach a covalent modification that "results in modulation of the association" between a pair of polypeptides. Therefore, the reference does not teach all elements of amended claim 1. As such, Sehr et al. does not anticipate claim 1 as amended or claim 9 that depends from it. Applicants respectfully request that the §102(b) rejection over Sehr et al. be withdrawn.

Claim 17 is rejected under 35 U.S.C. §102(b) as allegedly being anticipated by U.S. Patent No. 5,208,111 to Decher et al. Claim 17 recites "a polypeptide pair comprising a first polypeptide immobilized to a support and a second polypeptide bound to the first polypeptide, wherein (a) the binding of the polypeptides is detectable, and (b) modification of at least one of the polypeptides results in modulation of the binding".

The Office Action states that Decher et al. disclose a polypeptide pair immobilized to a support, wherein the second polypeptide is bound to the first polypeptide, and that the two

polypeptides disclosed are poly-Lysine and biotin. Applicants submit, as noted herein above, that biotin is not a polypeptide. Therefore, there is no "polypeptide pair," nor is there a "second polypeptide bound to the first polypeptide." Lacking those elements, Decher cannot anticipate claim 17. Applicants respectfully request that the novelty rejection of claim 17 over Decher et al. be withdrawn.

Claim 17 is rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5,773,592 to Mills. The Office Action states that Mills discloses a polypeptide pair immobilized to a support, wherein the second polypeptide is bound to the first polypeptide, with the two polypeptides disclosed being "an enzyme immobilized (claim 24) covalently bound to either insulin (claim 25) or tissue plasminogen activator (claim 26)." According to the Office Action, the modulation of chemiluminescence "through energy transfer and photochromic excitation is in association with the first and second polypeptides," allegedly anticipating claim 17. Applicants respectfully disagree.

Mills discloses and claims a chemical compound having the formula A-B-C, where: A is a chemiluminescent moiety which reacts with peroxides and oxygen free radicals and is capable of transferring energy from its own excited state to B; B is a photochromic moiety covalently bonded to A which receives energy from A to achieve an excited state; and C is a biologically active agent covalently bonded to B, wherein relaxation of the excited state of B causes heterolytic cleavage of the covalent bond between B and C, thereby releasing C from B. The compound is designed for regulated delivery of bioactive agents, which may comprise polypeptides. Claims 24-26 of the Mills patent, referred to in the Office Action, describe the situation in which the compound A-B-C is attached to a polymeric material to which an enzyme is immobilized (see column 138, lines 27-46). The recited enzyme, however, does not bind to or interact with C, but rather generates peroxide or oxygen free radicals by reaction with molecules in the ambient extracellular environment, the peroxide or free radicals serving to excite A, ultimately leading to release of C. Applicants submit that claim 17 requires "a polypeptide pair comprising a first polypeptide immobilized to a support and a second polypeptide *bound to the first polypeptide*" (emphasis added). If, for the sake of argument, the bioactive agent is a polypeptide being referred to by the Office Action as the "first polypeptide," Applicants submit that the "second polypeptide," the enzyme generating oxygen free radicals or peroxide, is not "bound to the first polypeptide." Therefore, Mills' disclosure does not describe all elements of

claim 17 and cannot anticipate claim 17. Applicants respectfully request that the 35 U.S.C. §102(e) rejection of claim 17 over Mills be withdrawn.

Applicants submit that in view of the foregoing amendments and remarks, all issues relevant to patentability raised in the outstanding Office Action have been addressed. Applicants respectfully request reconsideration of the claims.

Respectfully submitted,

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Date

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